



Severity and outcomes of hospitalised community-acquired pneumonia in COPD patients

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) is a frequent comorbidity in patients with community-acquired pneumonia (CAP). We investigated the impact of COPD on outcomes of CAP patients.

We prospectively studied the clinical presentation of 1,379 patients admitted with CAP during a 4-yr period. A comparative analysis of disease severity and course was performed between 212 patients with COPD, as confirmed by spirometry, and 1,167 non-COPD patients.

COPD patients (mean forced expiratory volume in 1 s $47.7 \pm 16.3\%$ predicted) were older and more likely to have previously received antibiotics (37.1% versus 28.3%; $p < 0.01$) than those without COPD. They presented with more severe respiratory failure (arterial oxygen tension/inspiratory oxygen fraction 270.4 versus 287.8; $p < 0.01$) and more severe pneumonia (pneumonia severity index 118.3 versus 108.5; $p < 0.001$) compared with non-COPD patients. However, COPD patients had less multilobar infiltration (44 (21%) versus 349 (30%); $p < 0.01$) and fewer pulmonary complications (24 (14%) versus 241 (24%); $p < 0.01$). A total of 89 (6.5%) patients died within 30 days. COPD patients had no significant difference in their 30-day mortality rate compared with non-COPD patients (nine (4.2%) patients versus 81 (7%); $p = 0.14$).

Despite worse clinical presentation, COPD patients had a similar mortality rate compared to non-COPD patients. Previous antibiotic treatment and the decreased incidence of pulmonary complications in COPD may account for these findings.

KEYWORDS: Chronic obstructive pulmonary disease, mortality, pneumonia

Chronic obstructive pulmonary disease (COPD) is a frequent comorbidity in patients hospitalised with community-acquired pneumonia (CAP), which may be explained mainly by the altered local and systemic immunity associated with this condition [1, 2]. Although this respiratory disease is a clear risk factor for CAP, it has not been shown to be a risk factor for mortality [3]. Accordingly, COPD has not been included as one of the five main comorbidities determining the risk of death in the Pneumonia Severity Index (PSI) [4].

A number of clinical and epidemiological studies have been carried out in order to determine the influence of COPD on the mortality of CAP patients, with conflicting results. Whereas two studies do not support COPD as a risk factor for death [3, 5], two other studies did show an excess mortality of CAP in patients with COPD [5, 6].

Another study in patients with severe CAP treated at an intensive care unit (ICU) also showed an increased risk of mortality [7]. One of the main problems of these studies is the lack of spirometric confirmation of COPD in some patients [4, 7].

Thus, the aim of this prospective study was to determine whether COPD is a risk factor for pulmonary complications and death in patients hospitalised due to CAP. For that purpose, we selected COPD patients with a diagnosis confirmed by spirometry.

METHODS

Patients

We prospectively studied 1,379 consecutive adults patients hospitalised with CAP during the period from 2004 to 2008 in the 850-bed tertiary care university hospital (Hospital Clinic,

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Barcelona, Spain). Of these, 212 patients with CAP had COPD confirmed by spirometry performed prior to admission. 60 patients were completely excluded from the study since, despite a history of COPD, no previous spirometry had been performed. Absence of COPD was confirmed by previous spirometry and/or clinical history (n=1,167). Moreover, we also excluded those smoking patients on inhaled corticosteroid (ICS) medication, but without asthma, to ensure the exclusion of not clearly diagnosed COPD.

Inclusion criteria were patients with a new radiographic infiltrate and at least two clinical symptoms suggestive of lower respiratory infection. We excluded patients with severe immunosuppression (patients with neutropenia after chemotherapy or bone marrow transplantation, solid-organ transplantation, HIV infection, corticosteroid treatment >20 mg prednisone equivalent per day for ≥2 weeks) and those with nosocomial pneumonia.

The study protocol was approved by the Ethical Committee of the hospital and all patients or their next of kin gave informed consent (registration number 2007/3543).

Definitions

We defined COPD according to the American Thoracic Society/European Respiratory Society criteria [8].

The classification of COPD severity was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: GOLD stage I was defined as a forced expiratory volume in 1 s (FEV₁) >80% predicted, GOLD stage II as FEV₁ between 50 and 80% pred, GOLD stage III as FEV₁ between 30 and 50% pred and GOLD stage IV as FEV₁ <30% pred [9].

Alcohol abuse was considered in cases with a current intake of >80 g·day⁻¹ of alcohol in males and >60 g·day⁻¹ in females [10]. Pulmonary complications were defined as parapneumonic pleural effusion, complicated parapneumonic pleural effusion and empyema requiring chest drainage, lung abscess and acute respiratory distress syndrome at presentation or developed during the first days of hospitalisation. Systemic complications were defined as the presence of renal failure and/or septic shock at presentation or developed during the first days of hospitalisation [11].

Mortality was evaluated 30 days after hospital admission, during follow-up.

Data collection

Demographic data, coexisting conditions, clinical information and laboratory values were collected at admission. The PSI was used to assess severity of pneumonia on admission [5]. Radiography was used to evaluate the number of lobes involved, the presence of cavitations, atelectasis and pleural effusions.

Follow-up variables were as follows: septic shock; need for invasive mechanical ventilation; pulmonary and systemic complications; systemic steroid treatment; previous antibiotic treatment in the last month; antibiotic treatment as well as duration of treatment; length of hospital stay (LOS) and 30-day mortality.

Samples for microbiological investigation were collected following a standard protocol: 1) blood cultures; 2) urine for *Streptococcus pneumoniae* and *Legionella pneumophila* antigen detection; 3) sputum in all patients when possible; 4) tracheobronchial aspirates in all intubated patients; 5) pleural fluid by thoracentesis; and 6) paired serology when possible to detect seroconversion (*i.e.* a four-fold increase in immunoglobulin G titres) for *Chlamydothyla pneumoniae* and *L. pneumophila* >1:128, *Coxiella burnetii* >1:80 and respiratory viruses (*i.e.* influenza viruses A and B, parainfluenza viruses 1–3, respiratory syncytial virus and adenovirus).

Statistical analysis

Categorical variables were described with counts and percentages. For continuous variables, the mean ±SD was presented. Relationships between categorical variables were studied using the Chi-squared test or Fisher's exact test when necessary. The comparison of continuous variables between two groups was carried out using the t-test for unpaired data once normality was demonstrated (Kolmogorov–Smirnov test); otherwise, the non-parametric test (Mann–Whitney U-test) was used.

The associations of the variables in general characteristics, severity of pneumonia, microbiological diagnosis and evolution of CAP with outcomes were assessed by using the following logistic regression models [12, 13].

The first analysis was based on a multivariate logistic regression model with COPD as the response; C-reactive protein (CRP) and LOS as covariates; and males, ICU admission, diabetes mellitus, pneumonia during previous year, smoking, alcohol, previous antibiotics, ICS use, previous corticoid therapy, PSI classes IV and V, CURB-65 (confusion of new onset, urea >7 mmol·L⁻¹, respiratory rate of ≥30 breaths·min⁻¹, blood pressure <90 mmHg systolic or diastolic blood pressure ≤60 mmHg, and age ≥65 yrs) ≥3, mechanical ventilation, shock, multilobar involvement, atelectasis, diagnosis, systemic complications, pulmonary complications and corticoid therapy as factors.

The second analysis was based on a multivariate logistic regression model with pulmonary complications as response, CRP as covariate, and males, diabetes mellitus, pneumonia during previous year, COPD severity, smoking, alcohol, previous antibiotics, corticoid inhalers, previous corticoid therapy, PSI classes IV and V, CURB-65 ≥3, diagnosis and corticoid therapy as factors.

The third analysis was based on a multivariate logistic regression model with systemic complications as response, CRP as covariate, and males, diabetes mellitus, pneumonia previous year, COPD severity, smoking, alcohol, previous antibiotics, corticoid inhalers, previous corticoids therapy, PSI classes IV and V, CURB-65 ≥3, diagnosis and corticoid therapy as factors.

The fourth analysis was based on a multivariate logistic regression model with mortality as response, CRP and LOS as covariates, and males, ICU admission, diabetes mellitus, pneumonia previous year, COPD severity, smoking, alcohol, previous antibiotic, ICS use, previous corticoid therapy, PSI classes IV and V, CURB-65 ≥3, mechanical ventilation, shock,

multilobar involvement, atelectasis, diagnosis and corticoid therapy as factors.

Variables that showed a significant result univariately ($p < 0.1$) were included in the corresponding multivariate logistic regression backward stepwise model to determine which of them were independently related to prognosis. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the models [12].

All analyses were performed with SPSS 16 for Windows (IBM, Sonek, NY, USA), and a two-sided p -value < 0.05 was considered to be statistically significant.

RESULTS

Clinical characteristics

We identified 1,379 patients hospitalised with CAP with a mean \pm SD age of 70 ± 17 yrs. The main characteristics of the patients, comorbidities and disease presentation are shown in online supplementary table 1.

Of the study population, 770 (56%) were smokers (271 ex-smokers and 499 current smokers) and 130 (9%) were living in nursing homes. 928 (67%) patients belonged to high-risk classes (PSI classes IV and V). The most frequent comorbidities were lung disease, chronic heart failure and neurological disease (table 1).

COPD was confirmed by spirometry in 212 (15%) patients. The mean \pm SD FEV₁ was $48 \pm 16\%$ pred. The classification of COPD patients into GOLD stages was as follows: stage 1, $n=13$ (6%); stage 2, $n=78$ (37%); stage 3, $n=98$ (46%); and stage 4, $n=23$ (11%).

The differences in baseline characteristics between COPD and non-COPD patients are summarised in table 1. COPD patients with CAP were significantly more likely to be male, were less likely to reside in nursing homes and were more likely to have a history of malignancy and high alcohol consumption. The rate of pneumonia in the previous year was also higher in COPD *versus* non-COPD patients (71 (34%) *versus* 198 (18%); $p < 0.01$). COPD patients were more frequently on antibiotics before admission (76 (36%) *versus* 322 (28%); $p=0.01$), ICSs (137 (65%) *versus* 148 (13%); $p < 0.01$) and previous oral steroids (27 (13%) *versus* 49 (4%); $p < 0.01$).

Non-COPD patients chronically using ICS before admission ($n=148$) were mainly affected by asthma (39%), bronchiectasis (15%), interstitial lung diseases (12%) and other chronic respiratory disorders, such as bronchial hyperresponsiveness or tuberculosis sequelae. 12 smoking patients on ICS medication but without asthma were excluded from the study. Similarly, non-COPD patients that had previously been administered oral steroids ($n=49$) were mostly affected by a chronic non-COPD respiratory disease (57%), such as asthma or bronchiectasis, or by other chronic diseases, such as neurological disease (31%) or a previous neoplastic disease (18%).

COPD patients had a higher mean PSI than non-COPD patients (118 *versus* 109; $p < 0.01$), but a similar proportion had a CURB-65 score ≥ 3 . They had a worse clinical presentation (respiratory rate and respiratory failure) at admission, but less fever and lower CRP levels (table 2). Likewise, radiographic extension was lower (multilobar infiltrates in 44 (21%) COPD patients *versus* 349 (30%) non-COPD patients; $p=0.01$),

TABLE 1 Clinical characteristics of the study population stratified according to the presence or absence of chronic obstructive pulmonary disease (COPD)

Variable	COPD	Non-COPD	p-value
Subjects n	212	1167	
Age yrs	73.4 \pm 8.8	69.4 \pm 17.9	0.49
Males	191 (90.1)	635 (54.4)	<0.01
Nursing home resident	12 (5.7)	118 (10.2)	0.04
ICU admission	21 (9.9)	125 (10.7)	0.73
Mechanical ventilation	10 (4.7)	61 (5.2)	0.76
Noninvasive mechanical ventilation	16 (7.5)	45 (3.9)	0.02
PSI	118.3 \pm 34.1	108.5 \pm 36.9	<0.01
PSI classes IV+V	159 (75.4)	769 (65.9)	0.01
CURB-65 ≥ 3	55 (27.5)	286 (25.7)	0.60
Comorbid conditions			
Heart failure	56 (26.4)	267 (23.0)	0.28
Chronic liver disease	12 (5.7)	48 (4.1)	0.32
Malignancy	28 (13.2)	66 (5.7)	<0.01
Renal failure	19 (9.0)	78 (6.7)	0.24
Neurological disease	46 (21.7)	318 (27.2)	0.09
Diabetes mellitus	55 (25.9)	234 (20.2)	0.06
Pneumonia during previous year	71 (33.8)	198 (17.5)	<0.01
COPD severity			
Mild	13 (6.1)		
Moderate	78 (36.8)		
Severe	98 (46.2)		
Very severe	23 (10.8)		
History of smoking [#]	202 (95.3)	568 (48.7)	<0.01
History of alcohol [†]	63 (34.2)	197 (17.9)	<0.01
Previous antibiotic in the last month	76 (37.1)	322 (28.3)	0.01
Previous ICS therapy	137 (64.9)	148 (12.9)	<0.01
Previous oral corticoid therapy	27 (12.9)	49 (4.2)	<0.01
Physical and laboratory data			
FEV ₁ % pred	47.7 \pm 16.3		
Confusion	51 (24.2)	326 (28.1)	0.24
Respiratory rate >30 breaths·min ⁻¹	89 (43.4)	385 (34.4)	0.01
Systolic blood pressure <90 mmHg	9 (4.3)	61 (5.3)	0.56
Heart rate >120 beats·min ⁻¹	27 (12.8)	161 (13.9)	0.67
Fever	157 (75.1)	960 (82.9)	0.01
Temperature $>39^\circ\text{C}$	18 (8.5)	148 (12.8)	0.08
$P_{a,O_2}/F_{i,O_2} < 250$	270.4 \pm 67.6	287.8 \pm 72.3	<0.01
CRP mg·dL ⁻¹	17.4 \pm 12.3	20.5 \pm 17.6	<0.01

Data are presented as mean \pm SD or n (%), unless otherwise stated. p-values in bold indicate statistical significance. ICU: intensive care unit; PSI: Pneumonia Severity Index; CURB-65: confusion of new onset, urea >7 mmol·L⁻¹, respiratory rate of ≥ 30 breaths·min⁻¹, blood pressure <90 mmHg systolic or diastolic blood pressure ≤ 60 mmHg, and age ≥ 65 yrs; ICS: inhaled corticosteroid; FEV₁: forced expiratory volume in 1 s; % pred: % predicted; P_{a,O_2} : arterial oxygen tension; F_{i,O_2} : inspiratory oxygen fraction; CRP: C-reactive protein. [#]: includes former and current smoking habit; [†]: includes former and current alcohol habit.

and pleural effusions (19 (11%) COPD patients *versus* 168 (16%) non-COPD; $p=0.07$) and empyema (0 *versus* 4%, $p=0.01$) were less frequent in COPD patients.

Aetiological diagnosis

Microbiological diagnosis was achieved in 537 (46%) patients. Blood cultures were diagnostic in 153 (16%) patients, with 19 (12%) having COPD. The most frequent microorganism in both groups was *S. pneumoniae*. Patients with COPD had more infections attributable to *Pseudomonas aeruginosa* but fewer attributable to *L. pneumophila* than non-COPD patients ($p<0.01$ and $p=0.04$, respectively) (table 2).

No specific microorganisms were significantly associated with pulmonary complications in the course of CAP, except for a trend towards a higher frequency of *P. aeruginosa* (five (3%) *versus* seven (1.5%) cases).

With regards to the chronic use of ICS, we observed that *Legionella* spp. were less frequent among patients using ICS (three (2%) *versus* 41 (8%) cases; $p=0.02$) while *P. aeruginosa* was more frequent (six (5%) *versus* six (1%) cases; $p=0.01$).

Disease evolution

Pulmonary complications

COPD patients developed pulmonary complications less frequently than non-COPD subjects (24 (14%) *versus* 241 (24%) patients; $p<0.01$). They less frequently presented with multilobar involvement (44 (21%) *versus* 349 (30%) patients; $p=0.01$), empyema (0 *versus* 41 (4%); $p=0.01$) and a trend to

less pleural effusion (19 (11%) *versus* 168 (16%); $p=0.07$) (table 3).

Pulmonary complications were more frequent in patients admitted to the ICU (49 (18%) *versus* 61 (7%); $p<0.01$) and in nursing home patients (33 (13%) *versus* 76 (8%); $p=0.03$), and in those with higher CRP levels at admission (23.9 ± 29.3 *versus* 18.9 ± 11.8 $\text{mg}\cdot\text{dL}^{-1}$; $p<0.01$).

In univariate analysis, diabetes mellitus, mild/moderate COPD, a history of pneumonia in the previous year, previous chronic therapy with ICSs and systemic steroids were associated with fewer pulmonary complications, while an increased CRP at admission and a known microbiological aetiology were associated with more respiratory complications (online supplementary table 2).

Multivariate analysis revealed that increasing CRP values ($+1$ $\text{mg}\cdot\text{dL}^{-1}$; OR 1.02, 95% CI 1.00–1.03) and a known microbiological aetiology (OR 1.6, 95% CI 1.1–2.1) were risk factors for pulmonary complications while diabetes mellitus (OR 0.62, 95% CI 0.41–0.95) and chronic use of ICSs (OR 0.54, 95% CI 0.35–0.84) were protective factors (online supplementary table 2).

Systemic complications

COPD and non-COPD patients developed a similar rate of systemic complications (25 (14%) *versus* 190 (19%) cases; $p=0.17$).

Systemic complications were more frequent in patients admitted to the ICU (27% *versus* 6%; $p<0.01$) and in those requiring mechanical ventilation (15% *versus* 2%; $p<0.01$). They had a higher PSI (IV–V, 87% *versus* 62%; $p<0.01$) and CURB-65 (≥ 3 , 51% *versus* 21%) classes, were more frequently males (66% *versus* 58%; $p=0.03$), were more frequently alcohol abusers (26% *versus* 19%; $p=0.02$) and suffered more renal failure (13% *versus* 6%; $p<0.01$).

At univariate analysis, a history of previous pneumonia in the previous year, prior antibiotic use and ICS use were associated with fewer systemic complications. By contrast, males, alcohol abuse, an increased CRP at admission, higher PSI (class IV and

TABLE 2 Microbiological diagnosis according to chronic obstructive pulmonary disease (COPD)

Microorganisms	COPD	Non-COPD	p-value
Subjects n	212	1167	
No diagnosis	117 (55.2)	630 (54.0)	0.74
Diagnosis	95 (44.8)	537 (46.0)	
<i>Streptococcus pneumoniae</i>	36 (37.9)	230 (42.8)	0.37
Virus spp. [#]	13 (13.7)	67 (12.5)	0.74
<i>Legionella pneumophila</i>	2 (2.1)	42 (7.8)	0.04
<i>Staphylococcus aureus</i>	0 (0.0)	17 (3.2)	0.08
<i>Chlamydomphila pneumoniae</i>	2 (2.1)	22 (4.1)	0.35
<i>Mycoplasma pneumoniae</i>	2 (2.1)	18 (3.4)	0.52
<i>Haemophilus influenzae</i>	1 (1.1)	12 (2.2)	0.45
<i>Pseudomonas aeruginosa</i>	7 (7.4)	5 (0.9)	<0.01
<i>Klebsiella pneumoniae</i>	0 (0.0)	5 (0.9)	1.00
<i>Moraxella catarrhalis</i>	0 (0.0)	2 (0.4)	1.00
<i>Escherichia coli</i>	2 (2.1)	7 (1.3)	0.54
Others	12 (12.6)	42 (7.8)	0.12
Polymicrobial pneumonia [†]	18 (18.9)	68 (12.7)	0.10

Data are presented as n (%), unless otherwise stated. p-values in bold indicate statistical significance. [#]: influenza A, influenza B, parainfluenza virus, respiratory syncytial virus and adenovirus. [†]: two microorganisms were found in 16 patients and three microorganisms were found in two patients in the COPD group; two microorganisms were found in 61 patients and three microorganisms were found in seven patients in the non-COPD group.

TABLE 3 Complications and outcomes of community-acquired pneumonia in patients with and without chronic obstructive pulmonary disease (COPD)

Variable	COPD	Non-COPD	p-value
Subjects n	212	1167	
Systemic complications	25 (14.3)	190 (18.6)	0.17
Pulmonary complications	24 (14.0)	241 (23.6)	0.01
Acute respiratory distress	1 (0.6)	23 (2.3)	0.15
Empyema	0 (0.0)	41 (4.0)	0.01
Pleural effusion	19 (11.0)	168 (16.5)	0.07
Septic shock	4 (2.3)	42 (4.1)	0.34
LOS days	10.2 \pm 8.8	10.3 \pm 9.5	0.49
Mortality	9 (4.2)	81 (7.0)	0.14

Data are presented as n (%) or mean \pm SD, unless otherwise indicated. p-values in bold indicate statistical significance. LOS: length of hospital stay.

V), higher CURB-65 (class ≥ 3), a known microbiological aetiology and previous intake of oral corticoid therapy were associated with increased systemic complications. COPD severity was not associated with the development of systemic complications (online supplementary table 3).

Multivariate analysis showed that classification into PSI class IV or V (OR 2.7, 95% CI 1.7–4.4), CURB-65 ≥ 3 (OR 2.8, 95% CI 1.9–4.1) and increasing CRP values (+1 mg·dL⁻¹; OR 1.03, 95% CI 1.01–1.04) were predictors of systemic complications (online supplementary table 3).

Outcomes

No differences were observed in ICU admission (21 (10%) *versus* 125 (11%); $p=0.73$) and in LOS (10.2 ± 8.8 *versus* 10.3 ± 9.5 days; $p=0.49$) between patients with and without COPD.

A total of nine patients with COPD died compared with 81 patients without COPD. The mortality rate of COPD patients was no different compared with the other CAP patients (4.2% *versus* 7%; $p=0.14$). After exclusion of nursing home patients from groups, the mortality rates were eight (4%) and 57 (5.4%), respectively ($p=0.52$).

In univariate analysis, the variables significantly associated with mortality at 30 days included admission to the ICU, smoking, alcohol, PSI class IV–V, CURB-65 ≥ 3 , mechanical ventilation, shock, multilobar infiltrates, corticosteroid systemic therapy during hospitalisation and LOS (table 4).

Multivariate regression analysis revealed mechanical ventilation (OR 4.2, 95% CI 2.2–8.2), PSI class IV and V (OR 25.4, 95%

CI 3.5–187.3), CURB-65 ≥ 3 (OR 2.5, 95% CI 1.6–4.1) and smoking to be protective factors (OR=0.58), so nonsmoking (OR 0.51, 95% CI 0.32–0.83) is independently associated with death (table 4).

Neither COPD nor the severity of COPD as defined using the classification in GOLD stages (I and II *versus* III and IV) was significantly associated with mortality either in the univariate or multivariate analyses.

DISCUSSION

In this study, patients with COPD and CAP did not differ in mortality rate from those without COPD. In fact, although COPD patients presented with more severe pneumonia, as reflected by significantly higher PSI scores, a trend towards an even lower mortality in COPD patients was observed.

The impact of COPD in patients hospitalised with CAP is controversial. In one prospective Spanish study, the mortality was 8%, which did not seem to be in excess of the rates reported for the general population [3]. Accordingly, in a subanalysis of a randomised clinical trial, the mortality was 8% and was not increased in patients with COPD hospitalised with CAP. However, the patient number was limited and the proportion of COPD patients was higher than usual (57%) [14]. In a large series of nonresponding CAP patients, MENENDEZ *et al.* [11] found that COPD was a protective factor against failure of treatment with initial antibiotics. Accordingly, it has recently been reported that, in a series including thousands of hospitalised CAP patients, the mortality of COPD was the lowest (10%) compared with several other comorbidities with a mortality of up to 25% [15]. Conversely, in a retrospective observational study from the USA including 744 patients, 215 of whom had COPD, there was a significantly higher 30- and 90-day mortality in COPD patients compared with those without COPD (10.6 *versus* 8.7%) [4]. Likewise, in a prospective multicentre study including 710 patients (244 with COPD), COPD was an independent risk factor for mortality in patients with CAP (OR 2.62) [6].

Besides potential biases in study designs, there are at least three important factors that might account for the conflicting results. First, the definition of COPD was not regularly done using spirometric measurements before admission for CAP, thus introducing a significant potential bias. Secondly, without spirometric measurements, no adjustment for COPD severity can be performed. Finally, inhaled and systemic steroids might fundamentally affect outcomes; however, variations in dosages and difficulties in documenting varying dosages over time make it extremely difficult to adequately control for this confounder [16]. An additional limitation of our study is the impossibility to have spirometry in non-COPD patients prospectively admitted for CAP.

In our study, patients were only defined as COPD patients when spirometries were available before admission, and we excluded patients with a clinical history of COPD and without spirometry. This approach substantially increases the validity of the diagnosis. Conversely, the availability of spirometries allowed the adjustment for COPD severity on multivariate analysis of complications and mortality. We made every effort to capture the history of inhaled and systemic steroid medications and also included this confounder in the multivariate

TABLE 4 Significant predictors of 30-day mortality from community-acquired pneumonia at univariate and multivariate analysis

Variable	Univariate		Multivariate [#]	
	OR (95% CI)	p-value	OR (95% CI)	p-value
ICU admission	2.3 (1.3–3.9)	<0.01		
Smoking	0.58 (0.38–0.89)	0.01	0.51 (0.32–0.83)	0.01
Alcohol	0.54 (0.27–1.05)	0.07		
PSI classes IV+V	23.6 (5.8–96.1)	<0.01	25.4 (3.5–187.3)	<0.01
CURB-65 ≥ 3	4.7 (2.9–7.4)	<0.01	2.5 (1.6–4.1)	<0.01
Mechanical ventilation	5.3 (2.9–9.6)	<0.01	4.2 (2.2–8.2)	<0.01
Shock	3.8 (2.1–6.8)	<0.01		
Multilobar involvement	1.7 (1.1–2.7)	0.01		
Systemic corticosteroids	2.3 (1.4–3.6)	<0.01		
LOS days (+1)	1.02 (1.00–1.03)	0.04		

p-values in bold indicate statistical significance. ICU: intensive care unit; PSI: Pneumonia Severity Index; CURB-65: confusion of new onset, urea >7 mmol·L⁻¹, respiratory rate of ≥ 30 breaths·min⁻¹, blood pressure <90 mmHg systolic or diastolic blood pressure ≤ 60 mmHg, and aged ≥ 65 yrs; LOS: length of hospital stay. [#]: Hosmer–Lemeshow goodness-of-fit test, $p=0.36$.

analysis. However, we could not exclude the hidden effects of dosage variations over time. Overall, we believe that we have taken these potential confounders into account as far as is possible. In the non-COPD group, COPD was discarded either by a previous spirometry result and/or from clinical history.

Patients with COPD had higher mean PSI classes at presentation but a similar CURB-65 score compared with patients without COPD, mainly because of older age and a higher percentage of male sex and number of comorbidities. Despite the higher PSI class, the mortality was lower. The same results were maintained when nursing home patients were excluded from the study. The paradox in COPD patients of more severe pneumonia by PSI score, but with better clinical outcome, could reflect the fact that PSI is possibly not a good marker of severity of CAP in COPD patients. Otherwise, the level of inflammatory response and the consequent lung injury could be better markers of disease severity in COPD patients. Two main reasons may account for this finding. First, it may be related to the fact that COPD patients more frequently received antibiotics before admission, and this has been shown to be protective against severe CAP [17, 18]. Accordingly, it has also been demonstrated in a large series of 388,406 CAP patients in Germany that death occurs most frequently within the first day after admission [19]. Conversely, the absence of differences in mortality between COPD and non-COPD patients did not change when we stratified COPD patients according GOLD stages. Secondly, despite a higher PSI in COPD patients, the extension of infiltrates and the amount of inflammatory response was lower. Conversely, parameters of acute respiratory failure (respiratory rate and arterial oxygen tension/inspiratory oxygen fraction ratio) were more severely compromised in COPD patients. This pattern of findings is best explained by the view that COPD patients might already experience acute respiratory failure with less pulmonary extension of pneumonia because of the pre-morbid chronic respiratory compromise. Moreover, this disproportionate effect of mild inflammatory compromise may account for a dilution of COPD as a risk factor of death [20, 21].

In accordance with this interpretation, COPD patients had fewer pulmonary complications at admission. Previous treatment with ICS failed to be an independent protective factor against mortality, but it was a protective factor against the development of respiratory complications at admission and during hospitalisation. Thus, we cannot discard the possibility that previous administration of ICS is not only a "marker of COPD", but that it may reduce lung inflammatory response resulting in fewer pulmonary complications [22]. In concordance with this hypothesis, different authors have clearly suggested that ICS could diminish CAP severity by modulating the local inflammatory response (lung microenvironment and macrophage activation) [23] and subsequent organ dysfunction [24, 25] and, possibly, could even reduce mortality rate [26, 27]. Our data do not confirm an association of ICS with mortality, but the observed protective effect against pulmonary complications clearly confirms the hypothesis of a positive influence of ICS on CAP severity.

Adjunctive therapy with corticosteroids can cause an attenuation of the inflammation and may improve outcome [28]. Systemic steroids have an inhibitory effect on cytokine

production, and have been proposed as a therapeutic option in pulmonary infection and severe sepsis, mainly in patients with adrenocortical insufficiency. In this study, the treatment with systemic steroids did not affect mortality.

In conclusion, this study showed comparable 30-day mortality between patients with spirometrically confirmed COPD and CAP, and patients without COPD, despite more severe pneumonia at admission (according to respiratory rate, respiratory failure and PSI). More frequent previous antibiotic treatment and the disproportion of amount of acute respiratory failure and radiographic extension in COPD patients are possible explanations for this paradox.

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STATEMENT OF INTEREST

None declared.

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